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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/277,074	03/26/1999	LINDA A. SHERMAN	TSRI433.1DIV	3068

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EXAMINER
DAVIS, MINH TAM B

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 06/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/277,074	SHERMAN, LINDA A.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this c mmunication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 May 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 47-51* is/are pending in the application.

4a) Of the above claim(s) *47-51* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Accordingly, claim 1 is being examined.

This application contains claims drawn to an invention nonelected with traverse in Paper No.8. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

The following are the remaining rejections.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

Rejection under 35 USC 112, first paragraph of claim 1 pertaining to lack of enablement for a method of specifically activating cytotoxic T lymphocytes *in vivo* in a subject having a tumor expressing HER-2/Neu, wherein said cytotoxic T lymphocytes could target or kill tumor cells expressing HER-2/Neu *in vivo* remains for reasons already of record in paper No.21.

Applicant argues that claim 1 does not contain the limitation "mice with a tumor expressing Her-2/neu".

Applicant's arguments set forth in paper No.23 have been considered but are not deemed to be persuasive for the following reasons:

Although claim 1 does not recite" mice with a tumor expressing Her-2/neu", claim 1 encompasses a method of specifically activating CTLs in a subject or an animal having a tumor expressing Her-2/neu, wherein said cytotoxic T lymphocytes are not

xenogeneic, and wherein the CTLs could target or kill malignant cells in said animal that express Her-2/neu protein.

It is however unpredictable that one can specifically activate CTLs having an affinity such that said CTLs could target or kill malignant cells that express Her-2/neu in an animal having a tumor burden that express Her-2/neu, due to self-tolerance as taught by Sherman et al, of record. As discussed in previous Office action, in a situation where Her-2/neu is a self-protein, such as in mice that have tumors that express HER/Neu, self-tolerance could eliminate T cells that are capable of recognizing Her-2/neu protein with high avidity. Thus unless tested, it is unpredictable that mice having tumors that express HER/Neu would produce CTLs specific for SEQ ID NO:10 with high affinity. Since the surviving CTLs would have low affinity to the claimed SEQ ID NO:10, one would not be able to predict that said CTLs with low affinity for SEQ ID NO:10 would be able to eliminate tumor cells *in vivo* (Sherman et al, of record, and the specification on page 101, lines 10-25). This inability of CTLs with low affinity to eliminate tumor cells *in vivo* would be even further exacerbated by tumors cells that either are not efficient in antigen presentation, similar to the tumor cell lines disclosed in the specification (p.106, lines 19-36), or tumor cells that do not express the specific tumor antigen due to an autochothonuous immune response (see discussion below, Cheever et al, of record, column 9, first paragraph). Further, as admitted by Applicant, after some period of time in the presence of tumor cells, T cells could lose their functional activity (specification, p.101). In addition, one could not extrapolate the *in vitro* tumor cell killing with *in vivo* tumor cell killing due to the following reasons: 1)

Characteristics of tumor cell lines *in vitro* are different as compared to primary tumor cells (Freshney et al, Dermer et al, of record). Further, although *in vitro* a tumor cell line can express the peptide of SEQ ID NO:10 from Her-2/Neu protein, the expression of a Her-2/Neu, that is originally expressed with initiation of a tumor, could be subsequently lost, because an effective autochothonuous immune response can convert a Her-2/Neu positive tumor to Her-2/Neu negative (Cheever et al, of record, column 9, first paragraph). Thus it is unpredictable that mice with Her-2/Neu tumor burden actually express or have adequate amount of Her-2/Neu protein on the tumor cell surface. Applicant however has not shown that in vivo primary tumor cells actually present or have adequate amount of the peptide of SEQ ID NO:10 on the cell surface, 2) I*n vitro* and *in vivo* environment is different, and 3) conditions for targeting tumor cells are different, wherein in *in vitro* the tumor cells are continuously exposed to the CTLs and in the presence of cytokines to increase the sensitivity of lysis by CTLs (Freshney et al, Dermer et al, of record). Further, as taught by Boon et al (of record), even if activated CTLs are significantly increased, the therapeutic success remains unpredictable due to inconsistencies in antigen expression or presentation by tumor cells (p.178, paragraph before last paragraph). Thus it is unpredictable that cytotoxic T lymphocytes that are not xenogeneic would be activated in an animal with a tumor burden that expresses Her-2/neu; wherein said cytotoxic T lymphocytes could target or kill primary malignant cells that express a Her-2/Neu protein *in vivo*.

In summary, in view of the above discussion, and further in view of the unpredictability of tumor vaccination and anticancer drug discovery, as overwhelmingly

evidenced by Ezzell et al, Spitler et al, Boon et al, Gura et al, Jain et al, Curti et al, and Hartwell et al (of record), it would have been undue experimentation to practice the claimed invention.

REJECTION UNDER 35 USC 103, NEW REJECTION

Claim 1 remains rejected under 35 USC 103, pertaining to obviousness over Grey et al, of record, in view of Cheever et al of record, Engleman et al, of record, and Yoshino, I et al, 1994, J Immunol, 152(5): 2393-400, for reasons already of record in paper No:21.

It is noted that this rejection only concerns activation of CTLs in mice without tumor burden.

Applicant argues that the data in table 24 *per se* do not support the conclusion of Grey et al that all peptides with a relative binding to A2 of greater than 0.01 are capable of inducing CTL, because the peptide WILRGTSFV has a relative binding affinity of 0.018 and yet has no CTL activity.

Applicant's arguments set forth in paper No.23 have been considered but are not deemed to be persuasive for the following reasons:

The peptide taught by Grey et al which is the same as the claimed peptide has A2 binding affinity of 0.1500.

Although the peptide WILRGTSFV has a relative binding affinity of 0.018 and yet has no CTL activity, from table 24 taught by Grey et al it seems that peptides having A2 affinity binding at or above 0.13 induce CTLs in transgenic mice. Thus although the

conclusion by Grey et al seems to be exaggerated to peptide with affinity as low as 0.01, from table 24 one would have expected that it is more likely than not that the peptide taught by Grey et al which is the same as the claimed peptide would induce specific CTLs in transgenic mice, since it has A2 binding affinity of 0.1500.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 703-305-2008. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, ANTHONY CAPUTA can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0916.

MINH TAM DAVIS

June 13, 2003

SUSAN UNGAR, PH.D
PRIMARY EXAMINER